Shock, Seizures, and Coma with Alkalosis During Mechanical Ventilation

KAYE H. KILBURN, M.D., *Durham, North Carolina*

EFFECTIVE THERAPY for patients with severe repiratory failure has produced new hazards which include increased acidosis during oxygen administration (1), pneumonia from breathing aerosols from contaminated nebulizers (2), cardiac arrhythmias associated with rapid reduction of carbon dioxide tension (3, 4), and hypochloremic alkalosis from rapid removal of carbon dioxide in chloride-depleted patients (5–7). Deterioration of mental and neurologic function has been associated frequently with increased acidosis due to reduction of alveolar ventilation (8–10). Recently confusion, seizures, and shock have been described in patients with severe alkalosis due to mechanical hyperventilation (6, 11, 12).

That severe alkalosis as well as severe acidosis are associated with cerebral dysfunction poses a diagnostic dilemma that can be resolved with certainty only by measurement of arterial blood pH. This paper describes several patients who developed tachypnea, confusion, anxiety, hypotension, movement disorders, seizures, and coma and died while their ventilation was controlled by intermittent positive pressure respirators. Awareness of this syndrome and repeated measurements of arterial blood pH and $Paco_2$ so that ventilation was adjusted to produce a normal hydrogen ion concentration rather than a normal $Paco_2$ have prevented sustained alkalosis and death of similar patients.

Received April 14, 1966; accepted for publication May 5, 1966.

From the Department of Medicine, Duke University Medical Center, and the Medical Service, Veterans Administration Hospital, Durham, N. C.

Portions of this study were presented before the Southern Sectional Meeting of the American Federation for Clinical Research, January 27, 1966, New Orleans, La.

Requests for reprints should be addressed to Kaye H. Kilburn, M.D., Associate Professor of Medicine, Duke University Medical Center, Durham, N. C. 27706.

CASE MATERIAL

Severe alkalosis was observed in 11 of 81 men treated for acute respiratory failure on a medical service during 2 years (Table 1). Respiratory failure was defined as arterial blood carbon dioxide tension ($Paco_2$) above 50 mm Hg or oxygen tension (Pao_2) below 55 mm Hg because patients beyond these levels usually required intensive treatment.

Ten of the 11 patients who developed severe alkalosis were between 64 and 77 years old (Table 1). These men had smoked one or more packages of cigarettes a day for at least 30 years. Loss of exercise tolerance, dyspnea, cough, sputum production, or orthopnea had existed for 6 to 48 years. Their hospitalizations were precipitated by severe shortness of breath, increased cough and sputum production, peripheral edema, or mental and neurological dysfunction.

Five patients had emphysema as manifested by large or relatively immobile chests, quiet breath sounds and roentgenographic evidence of flattened diaphragms, wide retrosternal spaces, radiolucent areas, or cysts. Their weights were 82, 83, 95, 96, and 143 lb. In addition to emphysema three other patients had scattered, dense fibrosis. They weighed 103, 119, and 139 lb. Three patients had chronic bronchitis with persistent cough and sputum production and prominent bronchial markings but otherwise normal chest roentgenograms. Two weighed 170 and 187 lb; one 210-lb man was obese.

Arterial blood carbon dioxide and oxygen

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TABLE 1. Neurologic Signs and Blood Gas Values in 14 Patients with Severe and Mild Sustained Alkalosis During Therapy of Respiratory Failure

Patient	Age	Pulmonary Disease*	(H^+) Initial	(H^+) Final	$Paco_2$ Final	Clinical	Manifestations†		Coma	Death
	yr		*nanomoles/liter*‡		*mm Hg*					
Severe alkalosis										
1	67	E, F	34.7	—	<30	A	T, As, M, S	—	+	+
2	74	E	39.8	22.4	27.5	A, C	—	—	—	+
3	46	A, E	40.7	24.5	33.8	A, C	T, As	Ar	—	+
4	67	E, F	33.1	26.8	39.3	A, C	T	H	—	+
5	70	E	35.5	27.3	44.2	A, C	T, As	—	+	+
6	68	E	54.9	28.2	41.0	A, C	T, M, S	H	+	+
7	68	E, F	53.7	28.8	38.6	A	As, S	H	+	+
8	70	B, O	56.2	28.8	61.0	A	T, S	H, Ar	+	+
9	64	E	41.7	29.2	41.8	A	T, As, M, S	H	+	+
10	77	B	41.7	29.5	34.0	A, C	T, As	—	—	+
11	68	B	62.3	30.2	49.0	A, C	T, As	H	+	+
Mild alkalosis										
12	41	E	42.2	30.9	45.0	A	—	—	—	+
13	72	E	36.3	31.6	45.8	—	T	—	—	—
14	68	F	35.9	33.1	34.0	—	T	—	—	—

* A = asthma; B = bronchitis; E = emphysema; F = fibrosis; O = obesity.
† A = anxiety; C = confusion; T = tremors; As = asterixis; M = myoclonus; S = seizures; H = hypotension; Ar = arrhythmia.
‡ Nanomoles/liter = 10^{-9} mEq/liter.

tensions and pH were measured in a gas tension meter (13) at 37 C within 10 min after obtaining samples. Initial arterial blood carbon dioxide tensions were from 43 to 83.5 mm Hg; two patients had $Paco_2$ of 122 and 132 mm Hg while receiving oxygen. Hydrogen ion concentrations were 33.1 to 56.2 nanomoles/liter except for 62.3 nanomoles/liter in one patient with superimposed hypercapnia during oxygen breathing. All patients were hypoxemic; Pao_2 were from 25 to 552 mm Hg. Three patients had oxygen tensions of 28.5, 32.4, and 33 mm Hg and were alkalotic at the time of admission. Mental and neurological dysfunctions occurred when arterial blood hydrogen ion concentrations were below 30.2 nanomoles/liter (pH 7.54); the lowest was 22.4 nanomoles/liter. Three patients who were less alkalotic with hydrogen ion concentrations of 30.9 to 33.1 nanomoles/liter had only tremors and anxiety; one died (Table 1). In three others alveolar ventilation was reduced when cerebral dysfunction and severe alkalosis were recognized; mental and neurological signs regressed, and two survived. The 11 severely alkalotic patients died: 9 after 7 to 18 days of mechanical ventilation, 1 with an expanding lung cyst after 4 days, and 1 chronically alkalotic asthmatic man on the ninety-first day of hospitalization.

TACHYPNEA, HYPOTENSION, AND ARRHYTHMIAS

In addition to manifestations of mental and neurologic dysfunction the patients with severe alkalosis had tachypnea, hypotension, and cardiac arrhythmias. All patients were tachypneic, often initiating 40 to 60 respiratory efforts/min despite coma. Breathing movements were regular and shallow, accompanied by flared nostrils and the use of accessory muscle for respiration. If respirators were triggered by these breaths, the duration of inspiration exceeded that of expiration; obstruction was greater during exhalation of course, and patients' chests remained nearly maximally inflated by positive pressure. Such breathing resembled a dog's panting. In several instances shifting individuals with rates greater than 30 to assisted (patient-controlled) ventilation from automatic cycled rates of 10 to 16 on a respirator preceded the development of hypotension and seizures.

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Six patients were hypotensive and were maintained on vasopressor drugs from several hours to 6 days. Cardiac arrhythmias occurred in two patients; one had atrial fibrillation, the other had chaotic heart action which included bigeminy and episodes of ventricular tachycardia. Three patients died during manipulation of airways, suctioning, or loss of the cuff from their endotracheal or tracheostomy tube in the airway, probably from arrhythmias associated with severe acute hypoxia.

ANXIETY AND CONFUSION AND COMA

The 11 patients had severe anxiety and 7 became irrational and confused while alkalotic. Anxiety was associated with hyperkinetic behavior which contributed to the difficulties of managing ventilation. Coma was usually preceded by confusion which gradually worsened and patients became disoriented with respect to time, place, and person. The sequence of these changes in Patient 6 is shown in Table 2. In seven patients mental function deteriorated to coma which often persisted until death. When hyperventilation was reduced by airway obstruction or by attempts to slow their breathing rate, several patients roused sufficiently from their coma once or twice to recognize and speak to their attendants. However, they became comatose as ventilation was increased.

TREMORS, ASTERIXIS, MYOCLONUS, AND SEIZURES

Disorders of movement were frequent in alkalotic patients. Nine had slow coarse tremors of their outstretched hands. Asterixis, the flapping tremor, which was demonstrated best with patient's arms extended and hands dorsiflexed, was observed in seven. Three patients had myoclonus, that is, spontaneous episodic motor activity of flexors. It often occurred in episodes, involved more than one extremity, and occasionally affected the head. Movements were rapid, paroxysmal, and uncontrollable and often the patient was unaware of them. Myoclonic jerks became generalized into seizures in three patients but two others had seizures without preceding clonus having been observed. Coma did not prevent myoclonus or seizures but abolished asterixis and tremors. After seizures blood pressure often decreased so that vasopressors were required to maintain it. However, in two instances hypotension apparently preceded seizures.

TABLE 2. Neurological Signs During a Shift from Acidosis to Alkalosis (Patient 6)

Hours	0	2	4	120
Neurological signs				
Confusion	0	+	+	+
Coma	++	+	0	0
Anxiety	0	0	+	+
Tremors	0	0	+	+
Hypotension	+	+	+	+
Asterixis-myoclonus	0	+	+	+
Seizures	0	0	0	+
Arterial blood				
H^+, *nanomoles/liter*	54.9	44.7	30.9	28.2
$Paco_2$, *mm Hg*	83.5	70.5	43.5	41

POSTMORTEM FINDINGS

The 11 patients with severe sustained alkalosis died, and autopsies were performed on 7. The lungs of six patients showed severe emphysema and two had necrotizing bronchitis. One patient with emphysema had, in addition, severe fibrosis and an acute myocardial infarction. Another patient had an expanded giant lung cyst with collapse of surrounding lung. Two patients had severe bronchopneumonia; one of these had generalized pulmonary edema. Abscesses of the lung were complicated by pneumothorax in two patients. No patient showed evidence of cerebral trauma, meningitis, encephalitis, recent cerebrovascular thrombosis, intracerebral bleeding, or subdural hematoma.

CASE REPORT

The history of a patient is described below to emphasize the typical sequence of events leading to sustained alkalosis and its complications.

Patient 6, a 68-year-old white man, was admitted with disorientation and fever. Two days before hospitalization he had lower chest pain and produced an increased amount of yellow sputum. Two and one half years before this admission he had been hospitalized for bilateral inguinal herniorrhaphy. At that time he was noted to have a cough, increased sputum production, and chest roentgenograms compatible with emphysema. Six months later he was admitted with a pneumonic infiltrate in the left lung, confusion, and disorientation. Arterial blood oxygen saturation was 35% and $Paco_2$ was 52 mm Hg. The patient was confused; he was unable to find the bathroom and return

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to his bed and attempted repeatedly to smoke the filter end of cigarettes. His mentation improved somewhat and he returned home.

At the time of his last admission he was disoriented and combative with a temperature of 103.4 F. The chest diameter was increased, and diaphragms were low and moved poorly. There were rales at the lung bases despite greatly decreased breath sounds and expiratory and inspiratory wheezes. Cardiac impulse was palpable in the midepigastrium. The liver was palpable 3 fingerbreadths below the right costal margin. Peripheral pulses were active. There was no edema or clubbing of the extremities. The patient was somnolent, confused, and disoriented with a coarse tremor and asterixis of the extended arms. Arterial blood oxygen tension was 39 mm Hg and $Paco_2$ 66.3 mm Hg. A tracheostomy was done and large amounts of yellowish mucus were aspirated. Parenteral antibiotics were administered. The patient remained disoriented but was able to follow simple commands until the eleventh hospital day when he was found in coma in the early morning. $Paco_2$ was 83.5 and Pao_2 54 mm Hg (Table 2). Controlled respiration was begun. The $Paco_2$ was maintained between 41 and 58 mm Hg with oxygen tensions usually above 100 mm Hg. Because of the high bicarbonate level, hydrogen ion concentration remained below 30 nanomoles/liter. On the sixteenth day the temperature rose to 104 F. The patient became persistently hypotensive and blood pressure could be maintained only with pressor drugs. He became tachypneic and comatose. Continuous controlled ventilation kept him alkalotic and hyperoxic. During coma he had a generalized seizure. Because seizures recurred, pressor drugs were discontinued. As the blood pressure fell, seizures recurred and the patient died.

Thus, a severely bronchitic man with emphysema and a past history of confusion associated with respiratory failure was admitted with hypercapnia and hypoxia. He became acidotic despite repeated tracheal suction. Therefore, a tracheostomy was performed and he was maintained on a respirator. He became hypotensive and comatose 3 days later. Hyperoxia and severe alkalosis were continued by mechanical ventilation. Seizures that began 4 days after coma were preceded by myoclonus and intractable hypotension. Autopsy showed severe bronchitis with formation of small abscesses, severe destructive departitioning of the lung, several small pulmonary emboli, hemorrhage into alveoli, and several areas of organizing pneumonia. There was right ventricular hypertrophy. Cerebral vessels appeared normal, and the brain showed no pathological changes.

Comment: Patients with severe acidosis or with severe alkalosis produced by rapid changes in carbon dioxide tension may show confusion, tremors, asterixis, and coma. In addition, somnolence and disorientation without shock are associated with acidosis (10). However, anxiety, myoclonus, hypotension, or shock and seizures are typical of alkalosis. Sustained alkalosis was invariably fatal in the present patients. In contrast the mortality was about 30% in patients who were treated for respiratory failure but did not develop sustained alkalosis. Acidosis and alkalosis cannot be differentiated with certainty by neurologic signs and the wrong therapy may be disastrous. Therefore, it is imperative to confirm or correct clinical impressions by analysis of pH and $Paco_2$ in the arterial blood. High bicarbonate levels and depletion of body chloride were frequent in patients who became alkalotic. This was attributed to several processes including the gradual loss of chloride during respiratory failure as bicarbonate was selectively reabsorbed, reduced chloride intake and losses from the body due to vomiting, gastric suction, and the effect of diuretics. The elevated plasma bicarbonate levels produced alkalosis when $Paco_2$ was restored to normal.

Signs of severe neurologic dysfunction, including myoclonic jerks, seizures, and coma (6, 11, 12), have been reported to occur during rapid reduction of carbon dioxide tension in patients with respiratory acidosis. These changes have most often occurred during or shortly after reduction of carbon dioxide by mechanical ventilation and have correlated with alkalosis in patients reported by Robin (6) and by Rotheram, Safar, and Robin (12). Also, changes in awareness and clonic movements have been described in patients with hypokalemic, hypochloremic alkalosis (7, 11). The absence of pathological changes in the

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brains of these patients at autopsy has suggested a biochemical rather than an anatomic lesion.

Three related mechanisms individually or together could account for the mental and neurologic changes which are associated with alkalosis. First, various organs have differing affinities for bicarbonate or at least differing rates of washout when carbon dioxide tension and hydrogen ion concentration are reduced. The brain is evidently one of the slowest. Certainly cerebrospinal fluid bicarbonate takes several days to equilibrate after a change of carbon dioxide, even in normal people. Second, hypocapnia and alkalosis reduce cerebral blood flow, an effect probably dependent on the latter. Third, the brain appears to be sensitive to intracellular alkalosis or at least to deprivation of circulation produced by alkalosis. The clinical similarity of the effects of alkalosis and hypoxia suggests that the reduction in blood flow with subsequent hypoxia may be the predominant effect. Also, the rapid restoration of function that follows increased blood carbon dioxide tension appears to be more consistent with improved blood flow. However, direct evidence for this is not available. In contrast, the effects of acute alkalosis due to spontaneous hyperventilation are mainly peripheral and transient.

Paresthesia of the limbs, twitching of the face, pursing of the lips, drawing of the fingers, and the feeling of a band around the head were attributed to acute hyperventilation half a century ago (14). These signs were associated with the effort syndrome, palpitations, anxiety, and hysteria (15, 16). Despite the troublesome sensations, dizziness, fainting attacks, and weakness, acute hyperventilation is usually self-limited, and chronic hyperventilation is usually mild and comparable to sensations experienced during acclimation to high altitudes (16). The importance of hyperventilation as a symptom of structural disease of the heart or lungs has been emphasized recently (16, 17). Although tetany, carpal pedal spasm, and other peripheral signs appear to be related to peripheral vasoconstriction produced by a sudden reduction in carbon dioxide tension, the disturbances of consciousness and movement that are most troublesome in acute hyperventilation reflect alterations in the central nervous system. As arterial blood carbon dioxide tension and hydrogen ion concentration decrease in human subjects, neuromuscular excitability is increased. This varies from augmentation of patellar reflexes and increased ventilatory response to carbon dioxide to tetany (18). Cortical electrical activity shifts toward slow waves and a delta rhythm is produced on the electroencephalogram (19). Rapid onset of altered consciousness, blurred vision, syncope, and slowing of the dominant waves on the electrocardiogram (EEG) during hyperventilation have been reported in normal subjects (19).

Prolonged hyperventilation has been reported to produce seizures or unconsciousness in susceptible individuals (20). Production of the same phenomena by sudden inflation of a cuff around the neck (21) or by 90 to 120 sec of breath-holding (22) suggested that cerebral hypoxia was the mechanism in common (22). When hypoxia was prolonged, the cortical rhythm on EEGs slowed progressively, and myoclonus, seizures, and decerebrate rigidity occurred (23). During hyperventilation there is a sufficient reduction in cerebral blood flow to produce cerebral hypoxia. Kety and Schmidt (24) showed that hyperventilation, which lowered $Paco_2$ from 45 to 26 mm Hg in normal subjects, reduced cerebral blood flow from 52 to 34 ml/100 g per min, and cerebrovascular resistance almost doubled. Breathing low-oxygen mixtures during hyperventilation speeded the onset of anxiety, confusion, and syncope and resulted in slow rhythms on the EEG. Conversely, the detrimental effects of hypoxia on consciousness were ameliorated if 5% carbon dioxide was

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added to the inspired gas (25). Thus, the cerebral effects of hypoxia and hypocapnia appeared to be additive. It has been shown, however, that young normal subjects who developed EEG slowing during hyperventilation compensated for hypocapnia ($Paco_2$ 22.3 mm Hg) sustained past 15 min so that their EEGs were normal at 1 hr (26). The mechanism for this apparent breakthrough or restoration of cerebral oxygenation is unknown. However, the mechanism could include epinephrine release resulting in hyperglycemia, because administration of glucose intravenously to subjects has been reported to block the EEG slowing caused by hypocapnia during hypoxia (27).

An adverse direct effect of high oxygen tensions on subcortical activity has been suggested by Donald (28) who noted myoclonic seizures and muscle twitching without EEG changes during brief exposures of normal subjects to oxygen tensions in excess of 1,250 mm Hg. However, prolonged exposure to oxygen tensions of approximately 500 mm Hg may not be comparable to exposure to the higher oxygen tension for shorter periods. Therefore, although it is doubtful that these observations can be applied to the phenomena observed in the present patients, hyperoxia and other factors may further reduce cerebral blood flow in alkalotic patients.

Individual susceptibility to respiratory alkalosis is undoubtedly modified by factors which affect cerebrovascular reactivity and cerebral function. These include narcotic, sedative, and tranquilizer drugs, hypoglycemia, cerebral arteriosclerosis, low systemic blood pressure, low cardiac output, reduced blood volume, diminished peripheral resistance, and previous cerebral ischemia or infarction. Engel, Ferris, and Logan (19) noted that cerebral function deteriorated earliest in those areas of the brain which had received previous insults or which had the least reserve of blood supply. Elderly patients' slow recovery from anesthesia, which is probably often complicated by hypoxia, has been attributed to cerebrovascular disease and previous ischemic insults to the brain (29). The elderly patients in the present report may have failed to compensate for hypocapnia that has followed severe hypoxia and hypercapnia because of such underlying disease. In addition, there may have been mechanical interference with cardiac output which reduced cerebral blood flow.

Anesthetized dogs showed a profound fall in blood pressure and developed cardiac arrhythmias together with vasoconstriction of skin and brain during mechanical hyperventilation (18). Also, cardiac output was reduced in anesthetized dogs and cats by mechanical hyperventilation at rapid rates, an effect that is probably related to interference with venous return to the heart rather than to the washout of carbon dioxide (18). It has been well recognized in human subjects that the reduction in cardiac output produced by the Valsalva maneuver is potentiated by hyperventilation (30). Rapid cycling of positive pressure respirators in the present patients may not have allowed sufficient time for intrapleural pressure to reach atmospheric during brief expiration, so that a Valsalva effect was sustained which lowered cardiac output and reduced cerebral blood flow. These factors could help to explain the impressive differences between the responses of various patients.

The objective of therapy in patients with respiratory failure, particularly those in whom serum bicarbonate levels are elevated, should be to restore a normal hydrogen ion concentration gradually regardless of the carbon dioxide tension, which may be nearer 60 than 40 mm Hg. The minute ventilation and arterial blood pH, $Paco_2$, and Pao_2 of patients maintained on respirators should be measured frequently so that oxygenation is maintained and carbon dioxide tension is reduced slowly. If alkalosis occurs, ventilation should be reduced, the dead space between the respirator valve

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and the patient increased, or 5% carbon dioxide in oxygen administered (12). It may be necessary to administer chloride to permit excretion of bicarbonate by the kidneys as $Paco_2$ is being reduced.

Summary

Sustained hyperventilation produced alkalosis and serious mental and neurological dysfunction in patients with respiratory failure who were treated with controlled ventilation after tracheal intubation. The syndrome included tachypnea, hypotension, anxiety, confusion, tremors, asterixis, myoclonus, seizures, coma, and fever. Apparently alkalosis critically reduces cerebral blood flow so that severe hypoxia is imposed on a brain whose function has been compromised by vascular and circulatory diseases. Such patients died unless their alkalosis was relieved. Mental and neurologic function improved in alkalotic patients after $Paco_2$ was raised by decreasing ventilation.

Summario in Interlingua

Le efficace tractamento de patientes in acute collapso respiratori, particularmente con respiratores mechanic, ha producite nove complicationes. Istos include sever acidosis a coma, pneumonia, arrhythmias cardiac, e alcalosis hypochloremic. Sever alcalosis esseva associate con anxietate, myoclono, choc, e convulsiones, a parte confusion, tremores, asterixis, e coma in 11 de 81 patientes tractate pro acute collapso respiratori per medio de ventilation regulate. Octo de iste homines de etate avantiate habeva emphysema e 3 habeva bronchitis. Le hypercapnia esseva leve o moderate ante le administration de oxygeno. Le differentiation inter alcalosis causate per hyperventilation e acidosis producite per hypoventilation require determinationes del pH del sanguine arterial viste que le dysfunctionamento neurologic associate con acidosis es simile a illo associate con alcalosis. Le nivellos seral de chloruro esseva basse, e illos de bicarbonato esseva elevate in tal patientes, de maniera que illes disveloppava frequentemente alte grados de alcalosis quando le tension de CO_2 esseva reducite al norma. Le objectivo del therapia deberea esser le restauration del oxygenation e del pH normal sin reguardo al tension de CO_2. Supplementos de chloruro es a vices necessari pro restaurar le concentration normal e pro meliorar le excretion renal de bicarbonato. Le dysfunctionamento neurologic in iste ben oxygenate patientes hypocapnic e alcalotic resimila illo in patientes con hypoxia cerebral. Insufficientia cerebro-vascular, reduction del rendimento cardiac, obstruction del fluxo sanguinee ad le pulmones, e un basse volumine de sanguine pare augmentar le signos cerebral de alcalosis.

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